

# Alzheimer's Dementia an Overview

General Concepts  
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## General Concepts

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## Epidemiology of AD

- AD accounts for 60-75% of all Dementias
- Dementia frequency doubles every 5 years from 1% in the 60-65 y/o to 35-45% in the 85+ group
- Currently 4million American are affected
- In 2040 over 9 millions will
- Estimated cost of care was 156millions in 2003

## Cognitive Loss Syndromes

- Mild Cognitive Impairment( amnestic, non amnestic)
- Neurodegenerative Syndromes( AD,Fronto-Temporal, Picks, C-J, Parkinson's, Lewy Body)
- Vascular Dementia
- Nondegenerative, non vascular( ETOH, Traumatic,autoimmunitary etc..)

## Dementias by Autopsy

- AD: 49%
- AD+CVD: 21%
- LB: 11%
- PD: 5%
- CVD:5%

## Diagnosing Alzheimer's Dementia

- National Institute of Neurological, Communicative Disorders and Stroke- AD and Related Disorders Association (NINCDS-ADRDA )
- DSM 4
- diagnostic accuracy: sensitivity 81-93%  
specificity 48-70%

## Protective Factors

- Active cognitive involvement;
- Physical exercise;
- Antioxidants( Omega3, Vit E,C);
- Modest Alcohol;
- Statins;
- NSAID

## Risk Factors

- Female gender; ApoE-4 genotype; family history; Hypercholesterolemia; Hyperhomocystenemia; Diabetes; Head Injury; Psychological stress; Hypertension; Smoking
- NonGenetic risk factors account for 50% of clinical variance (low education, hormone replacement therapy, use of statins and NSAID, metabolic syndrome, vascular risk factors, closed head trauma, ETOH and lack of physical fitness)

## Warning Signs

- Memory loss; Difficulties with familiar tasks; Language diff. ; Disorientation; decreased Judgment) Decreased abstract thinking; Misplacing objects; Mood/behavior changes; Personality changes; Loss of initiative

## Genetics

- Autosomal Dominant form( 3-5%) mutations in Chromosome 21,14 and 1 involved in regulation the APP
- Chromosome 19 encoding of ApoE-4 well established risk gene( late onset familial and sporadic AD); 60% of AD are ApoE4and respond deferentially to Abeta immunotherapy
- Chromosome 11 via SORL1

## Neuropathology

- Amyloid Plaques( beta amyloid, degeneration neurons surrounding and astrocytes + microglia
- Neurofibrillary Tangles( hyperphosphorylated tau protein in double helical shape)
- Atrophy

## Neuropathology of AD

- Accumulation of abnormally phosphorylated tau proteins in neurons( tangles)
- Accumulation of 42 aminoacid amyloid fragments in the neuropil( plaques)
- Vascular changes of blood vessels,small strokes and neuronal death

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## Neurotoxicity of Abeta

- Abeta( mostly 42) aggregates into toxic oligomers responsible for transmitter deficits and ultimately cell death
- Low Amyloid beta and high Tau protein is characteristic of AD

## Neuropathology of non AD

- AD: tau aggregation and amyloid aggregation
- Parkinsonian Dementias: alpha-synuclein aggregation
- Fronto-temporal lobar degeneration: ubiquitin and/or tau aggregation

## Alzheimer's with Lewy Bodies

- Possibly the 3<sup>rd</sup> most common form of dementia
- 15-25% of AD have Lewy bodies
- AD and LBD have lots of clinical similarities
- LBD differs: fluctuating cognition, recurrent visual hallucinations, systematized delusions and subtle parkinsonism
- LBD: patients tend to fall more, have syncope, are sensitive to neuroleptics

## Clinical Assessments

# MCI

- Memory: impaired
- Language: normal
- Visuospatial skills: normal
- Executive Functions: normal
- ADL: normal

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## Diagnostic Evaluation

- Neuropsychological Testing
  - Will give the definitive Dx.
  - Most useful in the evaluation of mildly impaired pt's which require evidence of both memory and cognitive difficulties
  - Also appropriate in Pt's with early onset dementia
  - Testing will characterize the extent of impairment, the type of dementia, and establish baseline cognitive function

## Diagnostic Evaluation

- Neuroimaging
  - MRI recommended as part of initial evaluation( PIB scan specific for Amyloid)
  - PET scans contribute to diagnostic specificity and has been recently approved by Medicare to differentiate between Alzheimer's dx and frontotemporal dementia.
  - Imaging most valuable in subacute onset (less than 1 year) and early onset pt's as well as pt's who have vascular risk factors or focal lesion findings.

## Clinical Scales

- MMSE or MOCA
- NPI( 12 items scale including delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor deficits, nighttime behaviors, appetite)
- ADAS-Cog ( memory, language and praxis)

## Diagnostic Accuracy of Tests

- Head CT: sensitivity 95%, specificity 40%
- Spect: sensitivity 90%, specificity 42-73%
- Pet scan: sensitivity 93%, specificity 63%
- CT scan and MRI useful in the diagnosis
- PET and Spect scan are not superior to clinical criteria
- Cognitive tests are essential

## Symptoms Clusters

- Depression
- Mania
- Psychosis
- Agitation
- Neurovegetative ( loss of appetite, sleep impairment, pain....)

## AD-Psychosis

## General Concepts

- 90% of AD patients develop behavior disturbances
- Behavioral signs and symptoms of dementia are protean and confusing
- Behaviors often do not meet criteria for established psychiatric disorders
- Behavior occur in clusters that vary with time

## Neurobiological Correlates of Psychosis in AD

- Reduced Serotonin in the cerebral cortex
- Decreased Acetylcholine function
- Cholinergic loss in frontal temporal cortex associated with delusions in AD
- Higher levels of Norepinephrine, higher levels of Beta Adrenergic receptors
- Recent Dopamine receptor studies: increased homozygosity for DRD1 and DRD3

## FDA Criteria for Agitation

- Poor impulse control
- Tension
- Excitement
- Uncooperativeness
- Hostility

## Clinical features influencing treatment

- Demographics and social factors
- Co-Occurring conditions
- Site Specific Issues

## Demographic and Social Factors

- Age
  - Early onset associated with more rapid decline and greater impact on families
- Gender
  - Women are more often effected than Men
- Ethnic and Cultural background
  - Influences presentation and families perception of decline
- Social Support
  - Pt's with active support from family, church, and community tend to decline slower

## Co-occurring Conditions

- Delirium-
  - Common to almost all psychotropic drugs
- Parkinson's Dx
  - Use of dopaminergic agents predisposes pt's to psychotic phenomena
- Cerebrovascular Dx
  - Can directly cause or contribute to dementia
- Frontotemporal Dementia
  - Pt's have significant alterations of personality and behavior

## Site-Specific Issues

- Home care
  - Social isolation of pt's and emotional and physical strain on caregivers contributes to depression for both
  - Use of home health aids, day care, and respite care may avoid these downfalls
- Day care
  - Gives social stimulation for pt's and break for caregivers.
- Long-Term care
  - Little difference in outcomes between specialized Alzheimer's units and general units.
  - Review the policy for use of physical restrains and antipsychotic medications

## Hospital Specific Issues

- Inpatient General Medical or Surgical service
  - Behavior problems due to disorientation
  - High risk of delirium
  - Pt's have difficulty understand and communicating pain, hunger and discomfort.
- General Psychiatric Inpatient Units
  - Very helpful in resolving acute exacerbations of psychosis, depression,
  - Allows both nonpharmacological and pharmacological interventions to be tried more readily and aggressively

## Somatic Treatments

- Treatments for Cognitive and Functional losses
- Treatments for Psychosis and agitation
- Treatments for Depression
- Treatments for Sleep Disturbance

## Cleveland Clinic TX Domains

- Cholesterol reduction, glucose control, blood pressure control, smoke cessation
- Physical Fitness: aerobic exercise 3/week
- Individualized cognitive rehabilitation
- Cognition enhancers: Cholinesterase inhibitors, Memantine

## Treatments for Cognitive and Functional losses

- Cholinesterase Inhibitors
  - Tacrine, Donepezil, Rivastigmine, Galantamine
  - 1 pt improvement on MMSE average
- Memantine
  - Evidence and FDA support use in moderate to severe dx. Little functional improvement
- Vitamin E
  - No evidence supporting improvement in function or cognition and may in fact contribute to higher morbidity and mortality
- Other agents
  - NSAID's, HRT, desferrioxamine, melatonin, ginkgo
  - All show little or no evidence of improvement on morbidity and may be more harmful due to side-effects.

## Treatments for Psychosis and Agitation

- Antipsychotics
  - No clinically significant differences in efficacy of first generation
  - Adverse effects often offset advantages in efficacy of second generation drugs when used in dementia pts.
- Benzodiazepines
  - Perform better than placebo but not as well as antipsychotics in reducing behavior problems
- Anticonvulsants
  - Carbamazepine in low doses has shown benefit in several case series and a few small trials.

## Use of Atypical Antipsychotics

- Some evidence that other psychotropics (SSRI, trazodone, anticonvulsants....) are more appropriate and safer in the initial management
- Psychosis is very common, atypicals play a major role.
- Decrease liability for Tardive dyskinesia
- More favorable side effects

## Atypicals- Risperidone

- Several case reports
- 3 randomized studies up to 12 weeks
- Open-label extensions
- Recommended dose is 0.5-1mg
- Aggressivity responded to higher doses
- Dose related increase in : EPS, somnolence, impairment of cognition

## Quetiapine in AD

- Outpatients
  - Outpatient studies have used a 25mg increment protocol
  - HICFA recommended max dose in Nursing Homes is 200mg/day
- Inpatients
  - Average dose 450mg
  - Rapid titration up to 200mg in 4 days
- Side Effects
  - Most common side effects: early onset sedation, orthostatism and dizziness
  - Incidence of EPS similar to placebo

## Olanzapine in AD

- Olanzapine augments antidepressant effects of Fluoxetine
- Olanzapine effective in mania
- Recommended dose 5-10mg
- No increase in EPS or Tardive Dyskinesia
- Side effects: somnolence

## Other Psychotropics

- Ziprasidone: no data on efficacy or safety. Potential cardiac side effects not studied
- SSRI: depressive co morbidity is high, they seem to have a role in AD with psychosis
- Anticonvulsants: Valproic acid and Carbamazepine commonly used. Topiramate could emerge as an alternative
- Trazodone: often used for mild tranquilization and for sleep promotion
- Buspirone: helps at times!!!
- Lorazepam: main rescue medication, worsens cognition and gait.

## Treatments for Depression

- Antidepressants
  - SSRI's equally effective and more tolerable than cyclic antidepressants and SNRI's in head to head trials
- ECT
  - Supported by several larger, prospective studies and one small retrospective chart review

## Treatments for Sleep Disturbance

- Available data does not suggest a specific course of action
- Small studies have looked at Bright light therapy, sleep hygiene, and improving physical activity during day times when pts are likely to nap, all with limited positive results
- Few pharmacological agents have been studied in this population. None with positive results.


## Cost Effectiveness of Treatment

- In the meta-analysis “**Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.**” in the journal Health Technology Assessment 2001; Vol. 5: No. 1 a review of 7 systematic reviews, 13 RCT's, and 9 economic studies found that: “**It is difficult to quantify benefits from the evidence available in the literature. Statistically significant improvements in tests such as ADAS-cog (Alzheimer's Disease Assessment Scale cognitive subscale) may not be reflected in changes in daily life.**”


## Summary

- Psychosis, aggressivity and agitation commonly seen in AD are protean and often confusing
- Medical and Pharmacological reasons for state dependent abnormal behaviors to be ruled out first
- Psychosis as a Trait to be considered if psychosis lasts weeks
- Conventional antipsychotics no longer first line choice
- Risperidone, Olanzapine and Quetiapine are effective alternatives. Side effects vary

## Future Tx



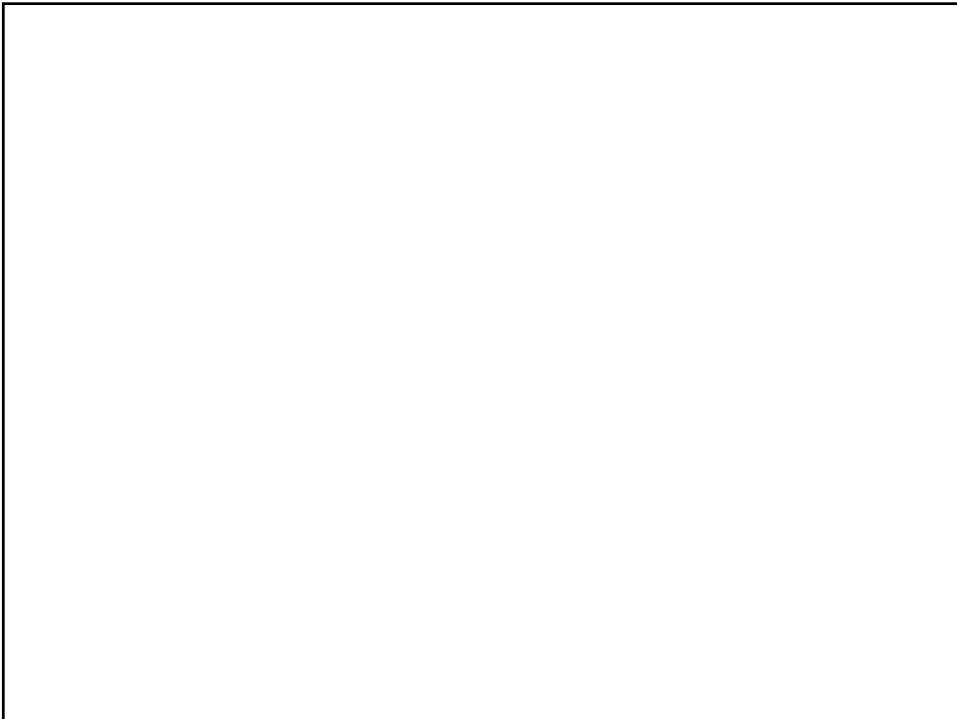
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## Costs

- Patient: health issues, medications
- Care givers: loss of income, emotional burden
- Social: disability benefits, day programs, home health, long term care, hospitalizations



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Thank you